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Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk.

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Abstract

Study question: Resistance to anti-tuberculosis medicines is a major public health threat in most countries of the former Soviet Union. As no representative and quality-assured information on the magnitude of this problem existed in Belarus, a survey was conducted in the capital city of Minsk.

Materials and Methods: Between November 2009 and December 2010, 156 and 68 consecutively diagnosed new and previously treated culture-positive tuberculosis patients residing in Minsk were enrolled in the survey. *Mycobacterium tuberculosis* isolates were obtained from each patient and tested for susceptibility to first- and second-line anti-tuberculosis drugs.

Results: Multidrug-resistant tuberculosis was found in 35.3% (95%CI: 27.7-42.8) of new patients and 76.5% (95%CI: 66.1-86.8) of those previously treated. Overall nearly one in two patients enrolled had multidrug-resistant tuberculosis. Extensively drug-resistant tuberculosis was found in 15 of the 107 multidrug-resistant tuberculosis patients (14.0%; 95%CI: 7.3-20.7). Patients under 35 years old have shown a 2 times higher odds of MDR-TB than those 35 and older.

Study answer: The findings of this survey in Minsk city are alarming and represent the highest proportions of multidrug-resistant tuberculosis ever recorded in the world. This study greatly contributes to the understanding of the burden of drug-resistant tuberculosis in urban areas of Belarus.

Keywords: epidemiology, extensively drug-resistant tuberculosis, multidrug-resistant tuberculosis, surveillance

Introduction

Tuberculosis (TB) in Belarus, as in most countries of the former Soviet Union, still represents an issue of serious public health concern [1-6]. Although over the past two decades the incidence rate of TB in the country has nearly halved, from 80 cases per 100,000 population in 1990 to 45 per 100,000 in 2010 [7], the emergence of forms of TB resistant to the most powerful medicines, including multidrug-resistant TB (MDR-TB) [1] [8] and extensively drug-resistant TB (XDR-TB)[2] [8], has been increasingly documented and may jeopardize the achievements made to date in controlling the community and nosocomial spread of *Mycobacterium tuberculosis* strains. Official national statistics, while not sufficiently representative nor quality-assured, suggest that the proportion of previously untreated (i.e., "new") TB cases having MDR-TB strains has grown from 8.8% in 2003 (169 cases) to 25.7% in 2010 (507 cases) [9-13].

Of the approximately 5,000 patients diagnosed with TB each year in the country, nearly 3,000 have a bacteriologically-confirmed diagnosis, with the remaining 2,000 being diagnosed only on clinical and/or radiological evidence [7]. Patients with drug-sensitive TB are treated with the standard regimen proposed by the World Health Organization (WHO) [14] only since 2009, with a treatment success rate for new smear-positive cases of 71% in that year, above the average of the WHO European Region [7]. A total of 1,576 patients with MDR-TB were started on treatment in 2010 in the country. Those patients are treated in one

[1] Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs [8].

[2] Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB plus resistance to any fluoroquinolones and at least one second-line injectable agent: amikacin, kanamycin and/or capreomycin [8].

of the 19 dedicated TB hospitals during the intensive phase of treatment (6-8 months) and then asked to continue their therapy in one of the 213 outpatient facilities for an additional 18-24 months, as per international recommendations [8,14-16].

Very high frequencies of MDR-TB have been documented in nearby countries, including Russian Federation [17], Ukraine [18], Lithuania and Latvia [19]; reliable data from neighbouring Pskov oblast in Russia found MDR-TB in 28% of new TB cases in 2008 [20]. Given that Belarus was one of the few former Soviet Union Republics without sufficiently representative and quality-assured data on the magnitude of drug-resistance, the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis decided to undertake a drug resistance survey following WHO recommendations [21]. The capital city of Minsk, with a population of 1.8 million people, was selected as the target area for this study. The survey aimed to investigate levels and patterns of resistance to first- and second-line anti-TB drugs among new and previously treated TB cases and to explore risk factors for the development of drug resistance. In this manuscript we present the results of this survey.

Materials and Methods

Between November 2009 and December 2010 a survey to investigate anti-TB drug resistance was implemented in the capital city of Minsk by the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis and the National TB Reference Laboratory with technical support from WHO and the Swedish Institute for Communicable Disease Control (Stockholm, Sweden), which acts as Supranational TB Reference Laboratory [22] for Belarus. The study was designed to generate representative information on drug resistance among all patients with TB in the capital city. All consecutive patients with newly diagnosed and previously treated culture-positive pulmonary TB residing in Minsk for 6 months or more and registered in any of the three TB city dispensaries were invited to take part in the study. Only patients residing in Minsk city for 6 months or more were considered eligible for enrolment to avoid the risk of including subjects living in other parts of the countries who could have travelled to the capital city after diagnosis to seek better health care. New patients were defined as those without a history of prior treatment with first-line anti-TB drugs (isoniazid, H; rifampicin, R; ethambutol, E; and streptomycin, S), or those having received prior treatment for <1 month; previously treated TB cases were those who had received prior first-line anti-TB treatment for 1 month or more [14,21]. Informed consent was obtained from patients before enrolment into the study. The following variables were collected for each patient through a clinician-led interview administered during sputum collection: sex, age, country of birth, treatment history (new/previously treated case, including subcategory of previous treatment), HIV status, education (university/college/secondary school/primary school or lower), size of household (number of persons living in the same house), history of imprisonment, and history of smoking in the past 5 years. Medical records were reviewed to confirm the reliability of the information on

previous treatment history gathered through the interview. A random sample of patients (nearly 40% of the total) was re-interviewed during later monitoring visits to assess the quality of the answers provided in the initial interviews. Re-interviews showed full concordance with treatment history information obtained during the initial interviews. Only patients with positive culture were included in the analysis. Patients with only clinical and/or radiologic diagnosis of TB, extrapulmonary TB cases, cases of TB caused by mycobacteria other than *Mycobacterium tuberculosis* and patients having already received more than one retreatment regimen were excluded. The Ethics Committee of the review board of the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis reviewed and approved the survey protocol.

Two sputum specimens were collected from each patient. Isolation and identification were performed on BACTEC MGIT 960 (Becton, Dickinson and Company, Franklin Lakes, NJ USA). Isolates of *Mycobacterium tuberculosis* were sent to the National TB Reference Laboratory at the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis for drug susceptibility testing using BACTEC MGIT 960 [23]. The following critical drug concentrations were used: H = 0.1 μg/l, R = 1.0 μg/l, E = 5.0 μg/l, S = 1.0 μg/l, kanamycin (Km) = 2.5 μg/l, amikacin (Amk) = 1.0 μg/l, capreomycin (Cm) = 2.5 μg/l, and ofloxacin (Ofx) =2.0 μg/l.

The routine external quality assurance system for drug susceptibility testing at the National TB Reference Laboratory includes annual proficiency testing and regular on-site monitoring missions by the partner Supranational TB Reference Laboratory. To further assure the quality of the survey results, a sample of susceptible and resistant strains was shipped to the Supranational TB Reference Laboratory in Stockholm for re-checking as per WHO

recommendations [21]. In the most recent proficiency testing exercise and in re-checking survey strains, concordance between the two laboratories was 100% for the most important first- and second-line drugs (H, R, Km, Amk, and Cm.).

Data were double-entered into EpiInfo (version 3.5.1; Centers for Disease Control and Prevention, USA) and analysed using STATA statistical software (Release 10.0, Stata Corporation, College Station, TX, USA). Pearson's $\chi 2$ statistics or Fisher's two-tailed test were used to compare categorical variables. All variables were studied in a univariate analysis; those with P values <0.05 were included in a multivariate logistic regression analysis. Confounding effects were checked using backward regression analysis (a cut off p value of <0.05 was used to exclude variables from the model). In all analyses, confidence intervals and p values were corrected for finite population and clustering effect.

Results

During the intake period a total of 465 patients were notified in the city of Minsk. Of them 235 (50.5%) met the inclusion criteria of the survey (culture-positive pulmonary TB). Drug susceptibility tests could be perforemd for 224 (95.3%) of these patients enrolled. Nine patients had to be excluded because of culture contamination (3.8%) and two because of growth of mycobacteria other than *Mycobacterium tuberculosis* (0.9%) (Figure 1). Of the remaining 224 patients, 156 (69.6%) were new TB cases and 68 (30.4%) were patients with a history of previous TB treatment; 157 (70.1%) were male. The median age was 43 years (range 19-87). Data on history of TB treatment and additional characteristics of the study population are shown in Table 1.

Of the 156 isolates from new TB cases, 87 (55.8%, 95%CI: 47.9-63.6) were resistant to at least one first-line drug and 55 (35.3%, 95%CI: 27.7-42.8) were found with MDR-TB. Resistance to H, R, E, and S in new cases is shown in Table 2. Among those with MDR-TB, 5.5% (95%CI: 0.0-11.7) had XDR-TB strains. Resistance to Ofx, Km, Amk, and Cm in these TB and MDR-TB cases is shown in Table 3.

Of the 68 isolates from previously treated TB cases, resistance to any first-line anti-TB drug was found in 56 cases (82.4%, 95%CI: 73.1-91.6) and MDR-TB in 52 cases (76.5%, 95%CI: 66.1-86.8). Resistance to H, R, E, and S in previously treated cases is shown in Table 2. Among those with MDR-TB, 23.1% (95%CI: 11.2-34.9) had XDR-TB strains. Resistance to Ofx, Km, Amk, and Cm in these previously treated TB and MDR-TB cases is shown in Table 3.

For 15 isolates (9 from new and 6 from previously treated TB cases) second-line drug susceptibility testing was not available due to test failure of BACTEC MGIT 960. Tests were not repeated as those isolates were not MDR-TB.

As expected, previously treated TB cases in whom treatment with second-line drugs had failed showed a significantly higher risk of MDR-TB compared to relapse cases, i.e., those that come back with TB after having been previously declared cured or having successfully completed treatment (Odds Ratio [OR] 10.6, 95%CI: 5.1-22.3, p value<0.001). Interestingly, default cases, i.e., those who come back with TB after having interrupted treatment, had also a significantly higher risk of MDR-TB compared to relapse cases (OR 2.9, 95%CI: 1.8-4.8, p value<0.001). Compared to new TB cases, however, relapse cases were found to have a significantly higher proportion of MDR-TB (OR 2.9, 95%CI: 1.2-7.7, p value=0.011), with 61.5% (95%CI 41.5-81.6) vs. 35.3% (95%CI 27.7-42.8) in new cases.

Overall among the 224 patients enrolled in the study, MDR-TB was found in 47.8% (95%CI: 41.2-54.4) (Table 2). Among these 14.0% (95%CI: 7.3-20.7) were found to have XDR-TB (Table 3).

Although 3 TB patients with HIV infection were registered during the study period, none were enrolled in the survey as their sputum specimens were culture negative.

As expected, history of previous anti-tuberculosis treatment was the strongest independent factor for MDR-TB (OR 7.4, 95%CI 4.3-12.7, p<0.001). Among new TB cases, the risk of MDR-TB in the age group up to 34 years old was 2 times higher than in the age group 35 years old and older (OR 2.0, 95%CI 1.3-3.1, p=0.002). Associations between MDR-TB and

sex, country of birth, education, size of the household, history of imprisonment, and smoking in the past 5 years were not found to be statistically significant (Table 4).

Discussion

This study has revealed extremely high levels of drug-resistant TB in the city of Minsk. The proportions of new and previously treated TB cases found to have MDR-TB (35.3% and 76.5%, respectively) are the highest recorded anywhere in the world in the history of the WHO Global Project on Anti-tuberculosis Drug Resistance Surveillance [20,24]. The study has also revealed worrisome proportions of XDR-TB among new TB cases (2.0%) and in previously treated cases (19.4%): proportions more common for MDR-TB in other parts of the world [20,24].

The very high frequency of drug-resistant forms of TB indicates the existence of serious problems in organization of TB treatment in Minsk, as in Belarus overall. The turbulent years following the dissolution of the Soviet Union were characterized by drug shortages and not-before-seen social problems and poverty. As a result, a significant pool of drug-resistant strains emerged that continues to limit the success of the National TB control programme today, still confronted by several challenges.

Firstly, the outpatient phase of TB treatment, and particularly MDR-TB treatment, is not managed strongly enough: in some locations where patients receive ambulatory treatment, costly second-line drugs are insufficient and supplied irregularly. Ambulatory patients on any treatment regimen - first or second-line - frequently default due to the inconvenience or cost of travelling to obtain drugs and missing work, as well as coexisting social problems, including untreated alcohol addiction, which is common among TB patients in this region of the world.

Secondly, diagnosis of drug-resistance is often a timely process, as solid culture and drug susceptibility testing methods are most commonly used in the country. More rapid diagnostic

methods such as liquid culture and line probe assays [25] are not yet widely implemented, and Xpert MTB/RIF [26] has not yet been introduced. Implementation of rapid diagnostics, while costlier than solid culture and conventional drug susceptibility testing, could provide critical information faster to clinicians, allowing the patient to start appropriate treatment regimens sooner and prevent acquisition of further resistance and limit transmission of resistant *Mycobacterium tuberculosis* strains.

Thirdly, infection control measures in TB hospitals and dispensaries, including administrative and individual protection measures, are frequently insufficient, resulting in transmission of strains from drug-resistant to drug-susceptible patients.

The magnitude of the problem of drug-resistant TB does not come as a complete surprise for the country, given its relatively advanced nationwide surveillance system that routinely tests for drug susceptibility in 22 laboratories (3 in the city of Minsk) and centrally collects data at the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis. This system has shown increasingly high proportions of drug resistance in recent years (e.g., 26.9% MDR-TB among new cases in Minsk in 2009) [9-12]. However, the study described herein has ensured high-quality of testing - centrally performed at the National TB Reference Laboratory and confirmed by the partner Supranational TB Reference Laboratory - and careful collection of accurate patient treatment history information.

The routine surveillance system reported considerably lower proportions of MDR-TB than those found in this study: 26.9% vs. 35.3% among new TB cases and 60.3% vs. 76.1% among previously treated cases [9-12]. The differences may be due to shortcomings in registration of patient treatment histories in the routine surveillance system, or potential weaknesses in laboratory performance of the other two laboratories that routinely perform

drug susceptibility testing in Minsk. The insights gained from the study will be able to strengthen the routine surveillance system.

When disaggregating previously treated TB cases by subcategory, frequencies of MDR-TB were found to be significantly higher among relapse cases than new TB cases - 61.5% vs. 35.3%, respectively. This difference reflects that either weaknesses may exist in procedures for declaring patients successfully treated - i.e. such patients were not successfully treated of TB in the first place, due to remaining drug-resistant bacteria - and/or that inadequate infection control measures may be commonly causing TB patients to be re-infected with their fellow patients' drug resistant strains during hospitalization.

A single data point in time, as has been provided in this survey, can not answer the question of whether the situation of drug-resistant TB is getting better or worse in the city of Minsk. However, the higher prevalence of MDR-TB among the younger age groups of previously untreated TB cases is an indication of a possibly increasing transmission of MDR-TB strains, as previously untreated TB cases from older age groups (found to have lower proportions of MDR-TB) may have been infected with strains decades ago. This hypothesis is supported national routine surveillance data that in recent years have shown a worsening situation of MDR-TB, with an increasing absolute number of MDR-TB cases. At the same time, the overall incidence rate of TB in the country has dropped [7], implying that the TB control programme is having considerable success at treating drug susceptible TB, but is challenged by a growing pool of drug-resistant patients who represent a reservoir of infection to others. The sharp increase in proportion of MDR-TB among new TB cases in Belarus reported by the national surveillance system - form 8.8% in 2003 to 25.7% in 2010 - can be attributed to a real growth in numbers of drug-resistant cases but also to the decrease in the number of

drug-susceptible TB cases and to the improvement in laboratory services in recent years that has resulted in greater access to diagnosis.

An important limitation of this study is that patients who had failed a standardized retreatment regimen for TB and were subsequently on other non-standardized regimens were excluded from the study. This was done in line with WHO recommendations to avoid including patients already started on treatment [21]. In most countries those cases are few but in Belarus, as in many other former Soviet countries, such cases (commonly called "chronic" patients) are common and have generally a high frequency of drug resistance. Disregarding such cases' contribution to the overall burden of drug resistance results in underestimating the gravity of the problem in Minsk.

Significant gaps exist in the geographic coverage of reliable anti-TB drug resistance surveillance in the former Soviet Union, including Kyrgyzstan, most of Ukraine, Uzbekistan, Tajikistan and Turkmenistan, and large swaths of Russia. It is therefore entirely possible that other settings in the former Soviet Union unknowingly have similarly high or even higher proportions of drug-resistant TB than what has been reported in Minsk. Additionally, a number of settings have only old data, and many countries with nationwide data lack precise data at the provincial or city level [20,24].

At the time of publication of this report, Belarus is undertaking a nationwide survey of drug resistance, knowing the value of the information gained from the Minsk survey and taking advantage of the experience gained. It is imperative that all countries recognize the importance of drug resistance surveillance as an integral component of TB control [27,28]. Measures need to be taken to strengthen laboratories and recording and reporting systems, and organize special surveys as needed, in order to establish drug resistance surveillance

systems that provide representative and accurate data for informed decision-making.

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Conflict of interests

None declared

Disclaimer

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Tables

Table 1. Characteristics of TB patients.

	Male		Female		Total		P value
	n	%	n	%	n	%	
Total	157	70.1	67	29.9	224	100.0	
Age group, years							0.000
up to 24	7	4.5	13	19.4	20	8.9	
25-34	32	20.4	22	32.8	54	24.1	
35-44	39	24.8	13	19.4	52	23.2	
45-54	52	33.1	9	13.4	61	27.2	
55-64	20	12.7	2	3.0	22	9.8	
over 65	7	4.5	8	11.9	15	6.7	
Country of birth							0.632
Belarus	150	95.5	63	94.0	213	95.1	
Abroad	7	4.5	4	6.0	11	4.9	
Treatment history							0.458
New	107	68.2	49	73.1	156	69.6	
Previously treated	50	31.9	18	26.9	68	30.4	

Table 2. Proportion and 95% confidence limits of resistance to first-line drugs among new, previously treated, and all TB cases.

Resistance	New cases (156) % (95% CI)	Previously treated cases (68) % (95% CI)	All cases (224) % (95% CI)
Any first-line drug	55.8 (47.9-63.6)	82.4 (73.1-91.6)	63.8 (57.5-70.2)
H	47.4 (39.5-55.4)	79.4 (69.6-89.3)	57.1 (50.6-63.7)
R	36.5 (28.9-44.2)	77.9 (67.8-88.1)	49.1 (42.5-55.7)
MDR	35.3 (27.7-42.8)	76.5 (66.1-86.8)	47.8 (41.2-54.4)
E	23.1 (16.4-29.8)	52.9 (40.8-65.1)	32.1 (26.0-38.3)
S	53.2 (45.3-61.1)	77.9 (67.8-88.1)	60.7 (54.3-67.2)

H: isoniazid; R: rifampicin; MDR: multidrug-resistant (resistance to isoniazid and rifampicin); E: ethambutol; S: streptomycin.

Table 3. Proportion and 95% confidence limits of resistance to second-line drugs among new, previously treated, and all MDR-TB cases, and among new, previously treated, and all TB cases.

	Cases with MDR-TB			All cases with TB		
Resistance	New (55) % (95% CI)	Previously treated (52) % (95% CI)	All (107) % (95% CI)	New (n tested) % (95% CI)	Previously treated (n tested) % (95% CI)	All (n tested) % (95% CI)
Ofx	14.5 (4.9-24.2)	46.2 (32.1-60.2)	29.9 (21.1-38.7)	(147) 6.1 (2.2-10.0)	(62) 38.7 (26.2-51.2)	(209) 15.8 (10.8-20.8)
Kn	18.2 (7.7-28.7)	36.5 (23.0-50.1)	27.1 (18.5-35.7)	(147) 7.5 (3.2-11.8)	(62) 32.3 (20.3-44.2)	(209) 14.8 (10.0-19.7)
Amk	16.4 (6.3-26.5)	26.9 (14.5-39.4)	21.5 (13.6-29.4)	(147) 6.8 (2.7-10.9)	(62) 24.2 (13.2-35.2)	(209) 12.0 (7.5-16.4)
Cm	16.4 (6.3-26.5)	25.0 (12.8-37.2)	20.6 (12.8-28.3)	(144) 6.9 (2.7-11.1)	(61) 21.3 (10.7-31.9)	(205) 11.2 (6.9-15.6)
Injectable agents	18.2 (7.7-28.7) (55)	36.5 (23.0-50.1) (52)	27.1 (18.5-35.7) (107)	(147) 7.5 (3.2-11.8)	(62) 32.3 (20.3-44.2)	(209) 14.8 (10.0-19.7)
XDR	5.5 (0.0-11.7)	23.1 (11.2-34.9)	14.0 (7.3-20.7)	(147) 2.0 (0.0-4.4)	(62) 19.4 (9.2-29.5)	(209) 7.2 (3.6-10.7)

Ofl: ofloxacin; Km: kanamycin; Amk: amikacin; Cm: capreomycin; Injectable agents: kanamycin and amikacin; XDR: extensively drug resistance (resistance to ofloxacin plus resistance to kanamycin and/or amikacin and/or capreomycin).

Table 4. Risk factors for MDR-TB.

			Univariate			Multivariate			
	Tested	% MDR	OR	95%CLs	p value	OR	95%CLs	p value	
Sex									
- male	157	48.4	REF						
- female	67	46.3	0.9	0.5	1.6	0.769			
Age group, years									
- up to 24	20	60.0	REF						
- 25-34	54	50.0	0.7	0.3	1.5	0.311	0.7	0.3	1.6	0.354
- 35-44	52	38.5	0.4	0.2	0.9	0.032	0.3	0.1	0.7	0.006
- 45-54	61	55.7	0.8	0.4	1.8	0.657	0.6	0.3	1.5	0.298
- 55-64	22	50.0	0.7	0.3	1.7	0.389	0.7	0.2	1.8	0.416
- 65 or more	15	20.0	0.2	0.1	0.5	0.003	0.1	0.0	0.4	0.001
Country of birth									
- Belarus	213	48.4	REF						
- abroad	11	36.4	0.6	0.2	2.1	0.441			
Treatment history									
- new	156	35.3	REF						
- previously treated	68	76.5	6.0	3.1	11.4	0.000	7.4	4.3	12.7	0.000
Education									
- university	21	47.6	REF						
- college	96	54.2	1.3	0.5	3.3	0.587			
- secondary school	100	43.0	0.8	0.3	2.1	0.698			
- primary school or lower	5	40.0	0.7	0.1	5.3	0.759			
- unknown	2	0.0	-	-	-	-			
Size of household									
- 1	29	55.2	REF						
- 2	59	47.5	0.7	0.3	1.8	0.497			
- 3	65	41.5	0.6	0.2	1.4	0.222			
- 4	39	51.3	0.9	0.3	2.2	0.751			
- 5 or more	25	48.0	0.8	0.3	2.2	0.599			
- unknown	7	57.1	1.1	0.2	5.7	0.925			
History of imprisonment									
- no	182	47.8	REF						
- yes	41	46.3	0.9	0.5	1.9	0.866			
- unknown	1	100.0	-	-	-	-			
Smoking in the past 5 years									
- no	65	50.8	REF						
- yes	158	46.2	0.8	0.5	1.5	0.535			
- unknown	1	100.0	-	-	-	-			

Figures

Figure 1. Selection of the study population.